

Combat Damage Control Resuscitation: Today and Tomorrow

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ABSTRACT

Damage control resuscitation is the resuscitation of the massively hemorrhaging patient to restore physiology and optimize hemostasis with the overall goal of increasing patient survival. Damage control resuscitation is most often used with damage control surgery. In addition to the transfusion of blood components to optimize hemostasis, the concept of “permissive” hypotension is used to decrease the bleeding from uncontrolled bleeding points, the patient is warmed to avoid the coagulopathic effects of hypothermia, and severe acidosis is treated in an attempt to avoid coagulopathic and physiologic deterioration. The future of damage control resuscitation will most likely involve the refinement and customization of blood components for the individual patient and application of the principles of damage control resuscitation in the prehospital arena.

1.0 DAMAGE CONTROL RESUSCITATION

Damage control resuscitation is the method of, substances used, and amount of intravenous infusion used in conjunction with damage control surgery to optimize survival with the goal of “directly addressing the early coagulopathy of trauma” [1]. To understand damage control resuscitation fully, one must appreciate and understand the epidemiology of combat wounding, prehospital combat resuscitation, and damage control surgery — especially as practiced by military personnel in the combat zone.

1.1 Combat Demographics

From a retrospective analysis, the majority of “potentially survivable” injuries resulting in death on the battlefield and after reaching a surgical facility are due to hemorrhage [2-4]. In combat, hemorrhage is the cause in 83% to 87% of all such “potentially survivable” deaths. Of these deaths, approximately 50% are due to noncompressible hemorrhage from penetrating truncal injury [3-4].

1.2 Prehospital Resuscitation on the Battlefield

Noncompressible injuries prehospital are currently managed by giving crystalloid or synthetic colloids intravenously after the onset of class III shock (cardiogenic) and by getting the casualty to a surgical facility as fast as possible. Combat medics are taught the principles of tactical combat casualty care (TCCC) for use on the battlefield [5]. Current guidelines (February 2009) specify the use of pulse character and mental status (in the absence of traumatic brain injury) to evaluate for shock and then to administer 500 cc of Hextend[®] intravenously if the casualty is in shock. This dosage is to be repeated as needed once in 30 minutes if the patient is still in shock as determined by the pulse character and mental status. Continued efforts to resuscitate must be weighed against logistical and tactical considerations and the risk of incurring further casualties. To minimize the effect of Hextend[®] and crystalloids on coagulopathy and blood pressure, we limit Hextend[®] to a total of 1 liter and recommend “hypotensive resuscitation.”

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14. ABSTRACT Damage control resuscitation is the resuscitation of the massively hemorrhaging patient to restore physiology and optimize hemostasis with the overall goal of increasing patient survival. Damage control resuscitation is most often used with damage control surgery. In addition to the transfusion of blood components to optimize hemostasis, the concept of permissive hypotension is used to decrease the bleeding from uncontrolled bleeding points, the patient is warmed to avoid the coagulopathic effects of hypothermia, and severe acidosis is treated in an attempt to avoid coagulopathic and physiologic deterioration. The future of damage control resuscitation will most likely involve the refinement and customization of blood components for the individual patient and application of the principles of damage control resuscitation in the prehospital arena.					
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After reaching a deployed surgical facility, the patient with penetrating truncal trauma undergoes an exploratory laparotomy or a thoracotomy or both to stop the hemorrhage. The surgical technique used with massive hemorrhage has been described as damage control surgery.

2.0 DAMAGE CONTROL SURGERY

Damage control surgery is based on a U.S. Navy term and process used to describe “the capacity of a ship to absorb damage and maintain mission integrity [6].” When a U.S. Navy ship or submarine has taken hostile fire, the sailors—at all costs and all urgency—immediately put out all fires and stop any flooding. The surgical analogy is to stop all hemorrhaging and gastrointestinal soilage as fast as possible.

The need for speed in severely injured trauma patients is to avoid the trauma “lethal triad.” The lethal triad comprises the vicious cycle of hypothermia, acidosis, and coagulopathy [7]. The acidosis is from hypovolemic shock and inadequate tissue perfusion [8]. Hypothermia is from exsanguinations and loss of intrinsic thermoregulation [9-10]. Coagulopathy is from hypothermia, acidosis, consumption of clotting factors and platelets, and blood loss [11-13]. Recent evidence points to activated protein C as playing a significant role in the “acute coagulopathy” of trauma [14]. Coagulopathy, in turn, causes more hemorrhage and thus more acidosis and hypothermia; so the vicious cycle continues (see figure 1). In full fruition, the vicious cycle of the lethal triad is almost uniformly fatal.

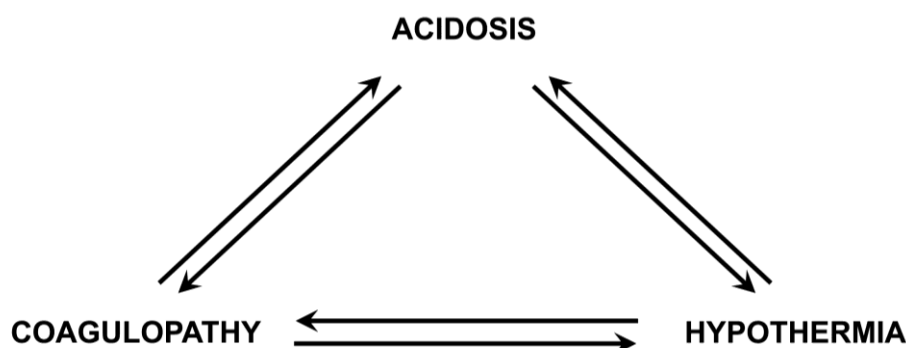


Figure 1: The “Vicious Cycle” of the “Lethal Triad”.

In 1993, in a landmark paper, Rotondo et al. reported the successful use of an abbreviated operation in trauma patients to avoid the lethal triad, coined “damage control,” with a mortality of 50% [15]. Many trauma centers have reported similarly successful results, and a damage control approach to the severely injured trauma patient is now commonplace and considered the standard of care [16-22].

While originally reported as an approach to severe abdominal trauma, the damage control process has evolved to cover all anatomic regions, including thoracic, neurologic, and extremity, especially in patients with injuries to multiple systems of the body [23-30].

3.0 DAMAGE CONTROL SURGERY IN THE CIVILIAN SETTING

Damage control by civilian surgeons is now well established as the standard of care for severely injured patients in the United States. The paradigm for damage control of injuries in civilians is based on a “damage

control trilogy” [31-32]. This trilogy comprises **abbreviated operation, resuscitation** in the intensive care unit, and return to the operating room for the **definitive operation**.

The goals of the “abbreviated operation” are primarily to stop all surgical hemorrhage and secondarily to stop all gastrointestinal succus soilage *in the shortest duration possible*. The patient is then brought to the intensive care unit to receive packed red blood cells, fresh frozen plasma, and platelets as needed using the tenets of damage control resuscitation limiting crystalloid fluids [33-74]. The patient is rewarmed, and full laboratory analysis is undertaken with the basic goal of bringing the patient’s physiology and temperature back to normal [35]. Each patient undergoing these operative procedures and care in the intensive care unit requires significant resources, both in personnel and logistics.

When the patient is hemodynamically near normal and stable with lab values, ventilator status, and body temperature in proximity to the previously noted goals, the patient is then returned to the operating for the “definitive operation.” This second operative procedure most often occurs 24 to 36 hours after the initial operation. The definitive operation would include bowel anastomoses or colostomy maturation, definitive vascular repair where an interposition vascular shunt had been previously placed, removal of hemostatic packing, and closure of abdominal fascia where feasible. The patient is then brought back to the intensive care unit, where postoperative care progresses toward the ultimate goal of discharge to the patient’s home or to a rehabilitation center.

The documented mortality for the damage control approach to patients requiring a damage control laparotomy is approximately 50% with a documented morbidity of approximately 40% [36].

4.0 DAMAGE CONTROL SURGERY IN THE U.S. MILITARY

Damage control of combat injuries involves up to 10 stages to allow for battlefield evacuation, surgical operations, and resuscitations [37]. Figure 2 is the basic outline for the multiple necessary stages in combat damage control.

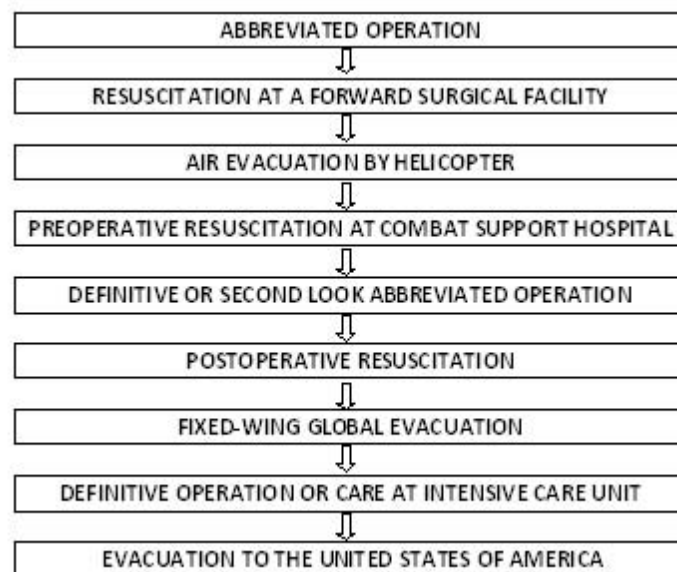


Figure 2: Surgery stages for damage control in the combat zone.

5.0 DAMAGE CONTROL RESUSCITATION

Damage control resuscitation is the resuscitation of the hemorrhaging patient, usually before and during damage control surgery. While most think of damage control resuscitation as the transfusion of blood components, it is actually an overall approach to treat the condition of severe hemorrhage and ameliorate the concomitant deleterious effects on physiology. In addition to the transfusion of blood components, the concept of “permissive” hypotension is used to decrease the bleeding from uncontrolled bleeding points, warming the patient to avoid the coagulopathic effects of hypothermia, and the treatment of severe acidosis [38].

The ratio of blood components that approaches the ratio found in whole blood is a ratio of fresh frozen plasma: packed red cells: platelets in a numeric ratio of 1:1:1 and would be a logical place to start when replacing the blood lost after trauma. Retrospective analysis of data from combat and civilian trauma patients who received a massive transfusion (>10 units of blood in 24 hours) indicates a survival benefit for patients receiving a high ratio of plasma (clotting factors) and platelets [39-45]. When determining the optimal clinical blood component ratio, one must keep in mind that from documented observations one will get a lower ratio than that which is targeted [46].

The clinical guidelines for resuscitation of combat-wounded patients in deployed U.S. surgical facilities in hemorrhagic shock requiring a massive transfusion recommend the infusion of fresh frozen plasma: packed red blood cells: platelets in a 1:1:1 ratio and the minimization of crystalloids and synthetic colloids [47].

Because of the unique austere challenges of logistics for deployed surgical facilities, blood components in sufficient supply to allow for the high ratios are at times not available. In this situation, the U.S. Military uses the transfusion of fresh whole blood. Retrospective reviews of outcomes in combat-wounded patients have revealed that the use of fresh whole blood is associated with improved survival [48]. Guidelines for the use of whole blood in damage control resuscitation also include the use of fresh whole blood transfusion at the discretion of the attending physician in patients with coagulopathy refractory to component therapy.

For severe acidosis, tromethamine; tris-hydroxymethyl aminomethane (THAM) is infused for a pH < 7.2 in accordance with the guidelines for damage control resuscitation. Current clinical practice guidelines for damage control resuscitation in the severely coagulopathic combat-wounded also include the use of recombinant factor VIIa at the discretion and judgment of the attending physician.

6.0 THE FUTURE OF DAMAGE CONTROL RESUSCITATION

Future advances in damage control resuscitation will most likely involve two major areas: customizing it to the individual patient with unique injury patterns and pushing it to the “left” onto the battlefield [49]. Now that we have defined the principles of damage control resuscitation, the time has come to start to “refine” it. Instead of blindly transfusing blood components in a fixed, empiric ratio, can we define the specific needs of the rapidly hemorrhaging patient and target blood components that are actually deficient in the intravascular space? Thromboelastography may offer the best option in the near term for defining the needs for transfusion and targeting blood components [50].

Thromboelastography has been shown to help guide transfusion of blood components during cardiac surgery and to decrease the overall postoperative transfusion requirements in this patient population [51]. Thromboelastography and rapid thromboelastography have been documented to be faster than conventional lab values and have documented improvement of coagulation with component therapy. Randomized trials to document any benefit, however, are lacking in the trauma population [52-53]. The future refinements of

damage control resuscitation will most likely need prospective, randomized trials based on algorithms guided by thromboelastography.

Bringing the principles of damage control resuscitation as far forward onto the battlefield is also a logical goal in the near term. All studies of prehospital crystalloid in trauma patients have revealed no benefit or harm [54, 55].

Damage control resuscitation in robust surgical facilities, using blood products and minimizing synthetic colloids and crystalloids coupled with permissive hypotension and thermoregulation will be the goals of far-forward resuscitation. Packed red blood cells by themselves dilute the other components, including clotting factors and platelets; and young healthy trauma patients can tolerate relatively low hemoglobin levels [56-58]. Platelets have a fragile existence, and the challenge of the deleterious effects of hypothermia and acidosis in severe shock may limit the utility of early infusion in the prehospital arena [59]. Plasma represents a colloid fluid for intravascular volume replacement, which also provides clotting factors to potentially ameliorate coagulopathy [60-62]. Plasma is also an excellent buffer, with 25-50 times the acid buffering capacity of crystalloids [63]. Dried plasma, as infused on the battlefield in World War II, offers the best opportunity for evacuation platforms and possible battlefield infusion during prolonged evacuation situations in the near term [64, 65].

7.0 CONCLUSION

Damage control resuscitation is the transfusion of blood components in conjunction with methods to treat acidosis and keep the patient warm and relatively hypotensive to complement damage control surgery. The future of damage control resuscitation involves further refining it and customizing transfusion practices toward the individual patient. Bringing damage control resuscitation to the prehospital phase of trauma care will offer the opportunity to further advance the care of the patient who suffers trauma and hemorrhage on the battlefield or in the civilian environment.

REFERENCES

- [1] Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*; 2007; 62:307-310.
- [2] Martin M, OH J, Currier H, et al. An analysis of in-hospital deaths at a modern combat support hospital. *J Trauma*. 2009; 66:S51-S60.
- [3] Kelly J, Ritenour A, McLaughlin D, et al. Injury severity and cause of death from operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *J Trauma*. 2008;64:S21-S27.
- [4] Holcomb J, McMullin N, Pearse L, et al. Causes of death in U.S. special operations forces in the global war on terrorism 2001-2004. *Ann Surg* 2007;245:986-991.
- [5] Butler FK, Giebner SD, McSwain NE, eds: *Prehospital Trauma Life Support Manual- Military Edition: Tactical Field Care*. Akron, Mosby, Seventh Edition, In press.
- [6] Navy. Surface ship survivability. Navy War Publications 3-20.31. Washington, DC.: Department of Defense; 1996.

- [7] Parr MJ, Alabdi T. Damage control surgery and intensive care. *Injury*. 2004 Jul;35(7):713-22.
- [8] De Waele JJ, Vermassen FE. Coagulopathy, hypothermia and acidosis in trauma patients: the rationale for damage control surgery. *Acta Chir Belg*. 2002 Oct;102(5):313-6.
- [9] Eddy VA, Morris JA Jr, Cullinane DC. Hypothermia, coagulopathy, and acidosis. *Surg Clin North Am*. 2000 Jun;80(3):845-54.
- [10] Tsuei BJ, Kearney PA. Hypothermia in the trauma patient. *Injury*. 2004 Jan;35(1):7-15.
- [11] Martini W, Pusateri A, Uscilwicz J, Delgado A, Holcomb J. Independent contributions of hypothermia and acidosis to coagulopathy in swine. *J Trauma*. 2005;58:1002-1010.
- [12] Armand R, Hess JR. Treating coagulopathy in trauma patients. *Transfuse Med Rev*. 2003 Jul;17(3):223-31.
- [13] Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. *J Trauma*. 1997 May;42(5):857-61.
- [14] Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute Traumatic Coagulopathy: initiated by Hypoperfusion Modulated Through the Protein C Pathway? *Ann Surg*. 2007 May;245(5):812-818.
- [15] Rotondo MF, Schwab CW, McGonigal MD, et al. "Damage control": an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma*. 1993; 35:375-383.
- [16] Loveland JA, Boffard KD. Damage control in the abdomen and beyond. *Br J Surg*. 2004 Sep;91(9):1095-1101.
- [17] Kouraklis G, Spirakos S, Glinavou A. Damage control surgery: an alternative approach for the management of critically injured patients. *Surg Today*. 2002;32(3):195-202.
- [18] Hirshberg A, Mattox KL. Planned reoperation for severe trauma. *Ann Surg*. 1995 Jul;222(1):3-8.
- [19] Burch J, Ortiz V, Richardson R, Martin R, Mattox K, Jordan G. Abbreviated laparotomy and planned reoperation for critically injured patients. *Ann Surg*. 1992 May;215(5):476-83; discussion 483-4.
- [20] Sharp KW, Locicero RJ. Abdominal packing for surgically uncontrollable hemorrhage. *Ann Surg*. 1992 May;215(5):467-74; discussion 474-5.
- [21] Burch JM, Ortiz VB, Richardson RJ, Martin RR, Mattox KL, Jordan GL Jr. Abbreviated laparotomy and planned reoperation for critically injured patients. *Ann Surg*. 1992 May;215(5):476-83.
- [22] Johnson JW, Gracias VH, Schwab CW, et al. Evolution in damage control for exsanguinating penetrating abdominal injury. *J Trauma*. 2001;51:261-271.
- [23] Roberts C, Pape H, Jones A, Malkani A, Rodriguez J, Giannoudis P. Damage control orthopaedics: evolving concepts in the treatment of patients who have sustained orthopaedic trauma. *Instr Course Lect*. 2005;54:447-62.

- [24] Rotondo MF, Bard MR. Damage control surgery for thoracic injuries. *Injury*. 2004 Jul;35(7):649-54.
- [25] Rosenfeld JV. Damage control neurosurgery. *Injury*. 2004 Jul;35(7):655-60.
- [26] Hildebrand F, Giannoudis P, Krettek C, Pape HC. Damage control: extremities. *Injury*. 2004 Jul;35(7):678-89.
- [27] Moore EE, Thomas G. Orr Memorial Lecture. Staged laparotomy for the hypothermia, acidosis, and coagulopathy syndrome. *Am J Surg*. 1996 Nov;172(5):405-10.
- [28] Harwood PJ, Giannoudis PV, van Griensven M, Krettek C, Pape HC. Alterations in the systemic inflammatory response after early total care and damage control procedures for femoral shaft fracture in severely injured patients. *J Trauma*. 2005 Mar;58(3):446-52.
- [29] Wall MJ Jr, Villavicencio RT, Miller CC 3rd, et al. Pulmonary tractotomy as an abbreviated thoracotomy technique. *J Trauma*. 1998 Dec;45(6):1015-23.
- [30] Mashiko K, Matsumoto H, Mochizuki T, Takuhiro K, Hara Y, Katada S. Damage control for thoracic injuries. *Nippon Geka Gakkai Zasshi*. 2002 Jul;103(7):511-6.
- [31] Shapiro M, Jenkins D, Schwab CW, et al. Damage Control: Collective Review. *J Trauma*. 2000;49:969-978.
- [32] Kouraklis G, Spirakos S, Glinavou A. Damage control surgery: an alternative approach for the management of critically injured patients. *Surg Today*. 2002;32(3):195-202.
- [33] Parr MJ, Alabdi T. Damage control surgery and intensive care. *Injury*. 2004 Jul;35(7):713-22.
- [34] Spahn DR, Rossaint R. Coagulopathy and blood component transfusion in trauma. *Br J Anaesth*. 2005 Aug;95(2):130-9.
- [35] Moore E, Feliciano D, Mattox K. *Trauma*. 5th edition McGraw-Hill Pub. 2004.
- [36] Bashir MM, Abu-Zidan FM. Damage control surgery for abdominal trauma. *Eur J Surg Suppl*. 2003 Jul;(588):8-13.
- [37] Blackburn L. Combat Damage Control Surgery. *Crit Care Med* 2008;36:S304-S310.
- [38] Beekley A. Damage control resuscitation: A sensible approach to the exsanguinating surgical patient. *Crit Care Med* 2008; 36:S267-S274.
- [39] Holcomb JB, Jenkins D, Rhee P, et al. Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma. *J Trauma*. 2007 Feb;62(2):307-310.
- [40] Perkins JG, Cap AP, Spinella PC, et al. An Evaluation of the Impact of Apheresis Platelets Used in the Setting of Massively Transfused Trauma Patients. *J Trauma*. 2009 Apr;66(4):S77-S85.
- [41] Holcomb JB, Wade CE, Michalek JE, et al. Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients. *Ann Surg*. 2008 Sep;248(3):447-458.

- [42] Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb HB. The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital. *J Trauma*. 2007 Oct;63(4):805-813.
- [43] Dente C, Shaz B, Nicholas J, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. *J Trauma*. 2006;66:1616-1624.
- [44] Teixeira P, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. *J Trauma*. 2009;66:693-697.
- [45] Spinella P, Perkins J, Grathwohl K. et al Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. *J Trauma*. 2008; 64:S69-S77.
- [46] Riskin D, Tsai T, Risin L, et al. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg* 2009;209:198-205.
- [47] Theater Trauma System (JTTS) Damage Control Resuscitation Clinical Practice Guidelines (CPGs). Available at <http://www.usaisr.amedd.army.mil>.
- [48] Spinella P, Perkins J, Grathwohl K, Beekley A, Holcomb J. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma*. 2009;66:S69-S76.
- [49] Blackbourne LH. The next generation of combat casualty care. *J Trauma*. 2009;66:S27-S28.
- [50] Wade CE, Dubick MA, Blackbourne LH, Holcomb JB. It is time to assess the utility of thrombelastography in the administration of blood products to the patient with traumatic injuries. *J Trauma*. 2009 Apr;66(4):1258.
- [51] Shore-Lesserson L, Manspeizer HE, DePerio M, et al. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesthesia and analgesia* 1999;88:312-319.
- [52] Jeger V, Zimmermann H, Exadaktylos AK. Can RapidTEG accelerate the search for coagulopathies in the patient with multiple injuries? *J Trauma*. 2009 Apr;66(4):1253-7.
- [53] Johansson PI, Hansen MB, Sorensen H. Transfusion practice in massively bleeding patients: time for a change? *Vox sanguinis* 2005;89:92-96.
- [54] Dalton AM. Prehospital intravenous fluid replacement in trauma: an outmoded concept? *J R Soc Med*. 1995;88:213p-216p.
- [55] Bickell W, Wall M, Pepe P, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994 Oct 27;331(17):1105-9.
- [56] Murray DJ, Pennell BJ, Weinstein SL, Olson JD. Packed red cells in acute blood loss: dilutional coagulopathy as a cause of surgical bleeding. *Anesth Analg*. 1995 Feb;80(2):336-42.
- [57] Hirshberg A, Dugas M, Banez EI, Scott BG, Wall MJ Jr, Mattox KL. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. *J Trauma*. 2003 Mar;54(3):454-63.

- [58] Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999 Feb 11;340(6):409-17.
- [59] Zhang JN, Wood J, et al. Bergeron AL. Effects of low temperature on shear-induced platelet aggregation and activation. J Trauma. 2004 Aug;57(2):216-23.
- [60] Alam HB, Bice LM, Butt MU, et al. Testing of blood products in a polytrauma model: results of a multi-institutional randomized preclinical trial. J Trauma. 2009 Oct;67(4):856-64.
- [61] Shuja F, Shults C, Duggan M., et al. Development and testing of freeze-dried plasma for the treatment of trauma-associated coagulopathy. J Trauma. 2008 Nov;65(5):975-85.
- [62] Gonzalez EA, Moore F, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma. 2007;62:112-119.
- [63] Traverso LW, Medina F, Bolin R. The buffering capacity of crystalloid and colloid resuscitation solutions. Resuscitation 1985;12:265-270.
- [64] Hardaway R. Wartime treatment of shock. Mil Med. 1987;147:1011-1017.
- [65] Hess J, Thomas M. Blood use in war and disaster: lessons from the past century. Trans 2003;43:1622-1633.

